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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
ROMEO, D	
ART UNIT	PAPER NUMBER
1647	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/416,828	Ammons et al.
Examiner	**Art Unit**
David Romeo	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 12 Oct 1999 .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-10 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

5/31/11 6) ☒ Claim(s) 1-10 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

5/31/11 8) ☒ ~~Claims 1-10~~ _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 2

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Claims 1-10 are pending and being examined.

Claim Rejections - 35 USC § 112

2. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing heart rate irregularities, cardiac arrhythmias, hypotension, bradycardia, and respiratory depression associated with intestinal ischemia/reperfusion by administering BPI, does not reasonably provide enablement for treating adverse physiological effects associated with intestinal ischemia/reperfusion by administering a BPI protein product. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are directed to or encompass the treatment of any and all adverse physiological effects associated with intestinal ischemia/reperfusion by administering a BPI protein product. The specification at page 1, lines 7-8, teaches that gut ischemia/reperfusion is associated with profound cardiovascular and respiratory dysfunction that may lead to shock and death. A rat surgical model was used to evaluate the effects of BPI protein products on the physiological effects associated with intestinal ischemia/reperfusion (page 7, lines 24-26). After the SMA was occluded the rats received an intravenous bolus injection of $rBPI_{21}\Delta cys$ followed by a constant

infusion of 2 mg/kg/hr. The infusions continued until death. See page 8, full paragraph 2. Obviously, the adverse physiological effect of death associated with intestinal ischemia/reperfusion was not treated. Furthermore, ischemia/reperfusion injury is a complex process. Grace (u6)[1] discloses several different processes have been implicated in ischemia/reperfusion injury. See, for example, figure 1 at page 640. Grace also discloses ischemia reperfusion injury is a complex process that is mediated by the interaction of free radicals, endothelial factors, and neutrophils and no single approach has proved to be consistently effective in limiting damage (page 643, column 2, bottom). Sepsis is an adverse physiological effect associated with intestinal ischemia/ reperfusion. See Figures 8A and 8B of the specification and Caty (YY, cited by Applicants) at page 699, paragraph bridging columns 1-2. Sepsis and multi-organ failure are the primary causes of late morbidity/mortality after trauma and shock; during fluid resuscitation of trauma and shock ischemic tissues are reperfused. See Horton (v6), page 1515, paragraph bridging columns 1-2. Bone (w6) teaches the intractable nature of treating sepsis. See page 565, column 1, paragraph 2, wherein it states "All the trials for new therapies for sepsis conducted to date have failed to show efficacy". See page 565, column 1, paragraph 3, wherein it states "The problem has not been the therapies tested, but the underlying hypothesis

[1]Citations by the examiner are in an alphanumeric format, such as "(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

that massive uncontrolled inflammation is the dominant cause of sepsis." and on page 566, column 1 ".. for patients with sepsis, the predominant state may be pro-inflammatory, anti-inflammatory, or both" and anti-inflammatory therapy "... may actually have increased mortality". The intractable nature of sepsis, the uncertainty with regard to its etiology, hence its treatment, and the lack of diagnostic procedures to determine the appropriate course of therapy (see Bone, page 566, column 1, 2nd full paragraph) establish that the contemporary knowledge in the art would not allow one skilled in the art to use the claimed methods to treat any or all adverse physiological effects associated with intestinal ischemia/reperfusion. Furthermore, the administration of a BPI protein product appears to induce tachycardia, an adverse physiologic, hemodynamic, cardiac effect. See Figures 4A and 4B of the specification. The specification lacks guidance for treating tachycardia with an agent that induces tachycardia. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, and the unpredictability in the art, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention.

As used herein, "BPI protein product" includes biologically active polypeptide analogs or variants of either bactericidal/permeability-increasing protein or biologically active fragments thereof (page 4, lines 23-29). Biologically active analogs and variants of BPI include, BPI protein products wherein one or more amino acid residues have been replaced by a different amino acid (page 6, lines 10-12). There are no limits on the number and type of amino acids that may be

replaced. The claims encompass essentially any and all compounds that achieve the desired results, including those unrelated to BPI, because all of the amino acids in BPI could be replaced. The specification lacks guidance for making, and working examples of, compounds unrelated to BPI that achieve the desired results. Moreover, there is a lack of predictability in the art. Predicting structure, hence function, from primary amino acid sequence data is extremely complex and there doesn't exist an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. See Bowie (x6) page 1306, column 1, full paragraph 1, and Ngo (y6) page 433, full paragraph 1, and page 492, full paragraph 2. The skilled artisan is left to extensive experimentation wherein any and all random peptides are randomly tested and through trial and error experimentation is left to determine which peptides achieve the desired results. In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the full scope of the claimed invention. Using the term "BPI protein" instead of "BPI protein product" may overcome the rejection with respect to the scope of the term "BPI protein product".

3. Claims 1-7, 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to or encompass a "BPI protein product". As used herein, "BPI protein product" includes biologically active polypeptide analogs or variants of either bactericidal/permeability-increasing protein or biologically active fragments thereof (page 4, lines 23-29). Biologically active analogs and variants of BPI include, BPI protein products wherein one or more amino acid residues have been replaced by a different amino acid (page 6, lines 10-12). There are no limits on the number and type of amino acids that may be replaced. The specification exemplifies a "BPI protein product" with a BPI protein and a polypeptide $rBPI_{21}\Delta cys$ comprising the first 199 N-terminal residues of BPI, wherein the cysteine residue at position 132 is replaced by an alanine residue (page 6, lines 18-21). The claims are directed to or encompass a genus of "BPI protein products" The specification and claims do not indicate what distinguishing attributes are shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to BPI. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is

needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, BPI and $rBPI_{21}\Delta cys$ alone are insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus. Note that using the term "BPI protein" instead of "BPI protein product" may overcome the rejection with respect to the description of the term "BPI protein product".

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-7, 10 are indefinite because they recite the term "BPI protein product". Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "BPI protein product" an artisan cannot determine what additional limitations are placed upon a claim by the presence of this term. Note

that using the term "BPI protein" instead of "BPI protein product" may overcome the rejection with respect to the indefiniteness of the term "BPI protein product".

b. Claims 1-10 are indefinite because it is unclear what effect is intended by an "effective amount"; an intended use is not the same as an effect; in the absence of a recitation as to any effect, or a process step producing an effect, or an effective amount of the agent to cause an effect, it is unclear what effect can be inferred.

c. Claims 1-10 are indefinite because they lack a process step which clearly relates back to the claim preamble and it is unclear what process is to be achieved; an intended use is not the same as achieving a result; in the absence of a recitation as to any result, or a process step producing a result, it is unclear what result of the process can be inferred.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1-3, 6-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gathiram (C6, cited by Applicants) in view of Theofan (a6), and, if necessary, further in view of Boermeester (C4, cited by Applicants).

Gathiram teaches that LPS is a highly toxic component of the outer cell membrane of gram-negative bacteria; the intestinal mucosal barrier to endotoxin can be broken down by a wide variety of diseases and physical onslaught such as trauma and ischemia (pages 103-104, Introduction). Intestinal ischemia produced by the occlusion of the SMA may be of value in studying the possible benefits of antimicrobial and LPS-specific therapy administered by various routes for endotoxin mediated diseases (paragraph bridging pages 107-108). Gathiram does not teach administration of $rBPI_{21}\Delta cys$ to a subject suffering from the effects of intestinal ischemia/reperfusion.

Theofan teaches that lipopolysaccharide (LPS), is a major component of the outer membrane of gram-negative bacteria and consists of serotype-specific O-side-chain polysaccharide linked to a conserved region of core oligosaccharide and lipid A; LPS is an important mediator in the pathogenesis of gram-negative septic shock, one of the major causes of death in intensive-care units in the United States. See column 1, lines 10-20. Theofan teaches a polypeptide comprising the first 199 N-terminal residues of BPI, wherein the cysteine residue at position 132 is replaced by an alanine residue (column 3, lines 48-52). The polypeptide taught by Theofan is identical to the description of $rBPI_{21}\Delta cys$ in the instant Application (page 6, lines 18-

21). Theofan also teaches that it is resistant to dimerization and cysteine adduct formation (column 3, lines 30-35). Theofan also provides stable, homogeneous pharmaceutical compositions comprising rBPI protein in pharmaceutically acceptable diluents, adjuvants, and carriers, that are useful in the treatment of gram-negative bacterial infection and the sequelae thereof, including endotoxin-related shock and one or more conditions associated therewith, such as disseminated intravascular coagulation, anemia, thrombocytopenia, leukopenia, adult respiratory distress syndrome, renal failure, hypotension, fever, and metabolic acidosis. See column 4, lines 39-51. $rBPI_{21}\Delta cys$ provided significant protection against the lethal effects of the endotoxin (column 28, lines 35-37). Theofan does not teach administration of $rBPI_{21}\Delta cys$ to a subject suffering from the effects of intestinal ischemia/reperfusion.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to study the possible benefits of antimicrobial and LPS-specific therapy administered by various routes in a subject suffering from the effects of intestinal ischemia produced by the occlusion of the SMA, as taught by Gathiram, and to modify that teaching by administering $rBPI_{21}\Delta cys$, as taught by Theofan, to a subject suffering from the effects of intestinal ischemia produced by the occlusion of the SMA with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because intestinal ischemia produced by the occlusion of the SMA may be of value in studying the possible

benefits of antimicrobial and LPS-specific therapy administered by various routes for endotoxin mediated diseases.

With respect to the application of prior art references it is noted that claims only require administering an effective amount of a BPI protein product to a subject suffering from the effects of intestinal ischemia reperfusion, and it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to administer an amount of $rBPI_{21}\Delta cys$ sufficient to protect against the lethal effects of the endotoxin. No difference is seen between "an effective amount" and an amount of $rBPI_{21}\Delta cys$ sufficient to protect against the lethal effects of the endotoxin.

Boermeester teaches that systemic endotoxemia, possibly of gut origin, is a major cause of the post-operative hemodynamic and metabolic derangements following phx and that $rBPI_{23}$ can prevent these changes. Boermeester does not teach administration of $rBPI_{23}$ to a subject suffering from the effects of intestinal ischemia/reperfusion. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to study the possible benefits of antimicrobial and LPS-specific therapy administered by various routes in a subject suffering from the effects of intestinal ischemia produced by the occlusion of the SMA, as taught by Gathiram, and to modify that teaching by administering $rBPI_{21}\Delta cys$, as taught by Theofan, and, if necessary, to modify that teaching by treating hemodynamic and metabolic derangements with BPI, as taught by Boermeester, with a reasonable expectation of success. One of ordinary skill in the art would

be motivated to combine these teachings because endotoxemia, possibly of gut origin, is a major cause of the post-operative hemodynamic and metabolic derangements, and $rBPI_{23}$ can prevent these changes.

The invention is prima facie obvious over the prior art.

8. Claims 1, 4, 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gathiram (C6, cited by Applicants) in view of Theofan (a6) and, if necessary, further in view of Boermeester (C4, cited by Applicants), as applied to claim 1 above, and further in view of Caty (YY, cited by Applicants). Gathiram in view of Theofan and, if necessary, further in view of Boermeester teach administering an effective amount of $rBPI_{21}\Delta cys$ to a subject suffering from the effects of intestinal ischemia/reperfusion, as discussed above. Gathiram in view of Theofan and, if necessary, further in view of Boermeester do not teach administering an effective amount of $rBPI_{21}\Delta cys$ to a subject suffering from the effects of intestinal ischemia/reperfusion wherein the intestinal ischemia/reperfusion associated with either myocardial infarction or intestinal torsion. Caty teaches that intestinal ischemia/reperfusion is associated with the prompt release of endotoxin (page 699, paragraph bridging columns 1-2). Caty does not teach administering an effective amount of $rBPI_{21}\Delta cys$ to a subject suffering from the effects of intestinal ischemia/reperfusion wherein the intestinal ischemia/reperfusion associated with either myocardial infarction or intestinal torsion. However, it would have been obvious to one of ordinary skill in

the art at the time of Applicants' invention to administer an effective amount of $rBPI_{21}\Delta cys$ to a subject suffering from the effects of intestinal ischemia/reperfusion, as taught by Gathiram in view of Theofan, and, if necessary, further in view of Boermeester, and to modify that teaching by administering an effective amount of $rBPI_{21}\Delta cys$ to a subject suffering from the effects of intestinal ischemia/reperfusion wherein the intestinal ischemia/reperfusion associated with either myocardial infarction or intestinal torsion, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because it would have been prima facie obvious to one of ordinary skill in the art at the time of Applicants' invention to administer an effective amount of $rBPI_{21}\Delta cys$ to any and all subjects suffering from the effects of intestinal ischemia/reperfusion, wherein the intestinal ischemia/reperfusion is associated with any and all conditions, including either myocardial infarction or intestinal torsion, because intestinal ischemia/reperfusion is associated with the prompt release of endotoxin, a highly toxic compound, and $rBPI_{21}\Delta cys$ provides significant protection against the lethal effects of the endotoxin. The invention is prima facie obvious over the prior art.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 1-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 5578568. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are generic to and encompass the claims of the patent.

11. Claims 1-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6017881. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are generic to and encompass the claims of the patent.

Conclusion

12. No claims are allowable. Claims limited to treating a specific adverse physiological effect with a BPI protein may be allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 6:45 A.M. TO 3:15 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

OFFICIAL PAPERS FILED BY FAX SHOULD BE DIRECTED TO (703) 308-4242.

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
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MAY 27, 2001

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